Medical Food

for dietary management of major depression

Facts about H_2O

Natural water is a composition of isotopologues, i.e. water molecules different only in isotopic composition.

Four isotopologues account for ~100% of total water content: $H_2{}^{16}O$, $H_2{}^{17}O$, $H_2{}^{18}O$, and $H^{16}OD$.

~100% of deuterium (D) is incorporated into isotopologue $H^{16}OD$.

$H^{16}OD$ content (i.e. "deuterium content") is measured by isotope ratio mass-spectrometry or laser spectrometry and expressed as deuterium-to-protium ratio (D/H), in parts-per-million (ppm).

Hereinafter, $H^{16}OD$ is designated as HOD for the simplicity of the presentation.

Table 1. Content of Water Isotopologues in Ocean Water
(Vienna's Standard of Mean Ocean Water, VSMOW)

Isotopologue	Molar mass, g/mol	Content	
		Mol %	mM
$H_2{}^{16}O$	18	99.7317	55 405
$H_2{}^{18}O$	20	0.2000	105
$H_2{}^{17}O$	19	0.0372	19
$H^{16}OD$	19	0.0311	16

Rothman et al., J. Quant. Spectrosc. Radiat. Transfer, 1998, 60:665; 2003, 82:9

^1H= H, hydrogen with mass 1
^2H= D, hydrogen with mass 2 (deuterium)

^{16}O= oxygen with mass 16
^{17}O = oxygen with mass 17
^{18}O = oxygen with mass 18

HOD in Nature

HOD levels in natural waters may vary by 50% due to fractionation occurring in the hydrological cycle, a planetary scale evaporation-precipitation process.

- 97% of Earth's water is an ocean water, deuterium content of 155 ppm.
- 2% of water is held by glaciers of mostly Antarctica and Greenland, deuterium content of 85-125 ppm.
- 1% of water is a surface and ground water (i.e. available water) that can be easily tapped for human use, deuterium content of 140-155 ppm.

Note: A vast majority of people consume water having deuterium content of 140-155 ppm.

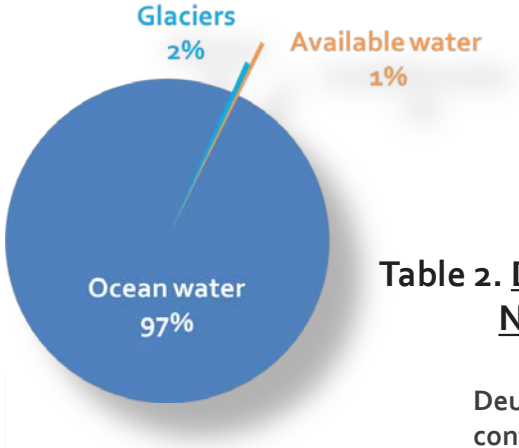


Table 2. Deuterium Content of Natural Waters

	Deuterium content, ppm	Max change to Ocean, %
Ocean	155	0
Pools of arid zones	175	+7%
Desalinated water	153-155	-1%
Rivers and Lakes	140-155	-10%
Greenland ice	125	-19%
Antarctic precipitations	85-117	-43%

How much HOD do people consume daily?

According to Dietary Guidelines for Americans, an average intake for total water is 3.7 liters per day for a man and 2.7 liters per day for a woman. Dietary Guidelines for Americans, 2005, U.S. Department of Health & Human Services.

96% of people in USA consume tap water with deuterium content of 140-155 ppm.

Deuterium content of commercially available bottled waters in US/Europe is more than 140 ppm (Table 3).

Based on these data, inescapable intake of HOD is estimated as about one gram per day per person:

0.7-0.9 gram per day for a woman

1.0-1.3 gram per day for a man

Table 3. Deuterium content of available bottled waters

Water source	Place of origin	D/H, ppm
Standard (Ocean water)	Ocean	155,76
Dubai tap water	Dubai	153,87
Smart Water	Coca-Cola	147,14*
Spring water, Stäfa	Switzerland	145,75
Henniez Mineral Water	Switzerland	145,47
Eptinger Mineral Water	Switzerland	145,20
Evian Mineral Water	France	144,83
Zurzacher Mineral Water	Switzerland	144,40
Farmer Mineral Water	Switzerland	143,35
Elmer Mineral Water	Switzerland	143,15
Adello Mineral Water	Switzerland	143,00
Valser Mineral Water	Switzerland	142,07
Spring water, Mainenfeld	Switzerland	141,76
Rhäzunser Mineral Water	Switzerland	141,36
Aproz Mineral Water	Switzerland	140,10
Standard (Antarctic precipitations)	Antarctica	89,90

Measured by Dr. Rolf Siegwolf, Paul Scherrer Institute, Switzerland
*AO ALMAZ LAB (Russia)

Ranges of deuterium content of natural water:

Range, ppm	Market	Who drink	Comments
140-155	96%	A vast majority of people n U.S.A. consume water, beverages, and food with such deuterium content every day.	Plain water
139-135	4%	People from regions far from ocean and sea in cold climate and in mountains consume such water every day. Water from Baikal lake is about 137 ppm deuterium content.	• People consuming such water are healthier at all ages. • It is not unique water, since minor part of population consumes such water.
135-89	~0%	People do not consume such water because the source is hard-to-rich places.	• Really unique water, since it is absent on mass market. • This water is unavailable by logistic reasons (e.g. Antarctica plateau). • People consuming such water would be more healthier than those consuming 135-155 ppm water.

Disorder prevalence vs. deuterium content of water

Disorder		Prevalence (%), < 140 ppm *vs.* >150 ppm	
		Absolute*	Relative
Mental disorders	Psychosocial Distress	3.0 vs. 5.5%	-45%
	Depression	7.1 vs. 10.0%	-29%
Metabolic disorders	Diabetes	6.7 vs. 9.8%	-31%
	Obesity	23.7 vs. 30.0%	-21%
Cardiovascular disorders	Hypertension	25.0 vs. 31.7%	-21%
	Coronary Heart Disease	5.4 vs. 6.9%	-22%
	Stroke	2.1 vs. 3.3%	-36%
	Myocardial Infarction	3.6 vs. 4.3%	-16%
Tooth Loss	Loss of 6 or more teeth	36.4 vs. 47.6%	-23%
	Complete tooth loss	17.4 vs. 23.5%	-16%

*Differs significantly for all shown disorders, p<0.05

Methods:

Based on State-by-State data from *Centers for Disease Control and Prevention (USA)* and *Survey data on deuterium content of tap water*, we measured the strength of association between deuterium content of water and prevalence of disorders using Pearson correlation analysis.

Results:

There is a significant linear correlations between deuterium content of tap water and rates of certain disorders, especially mental disorders.

Conclusion:

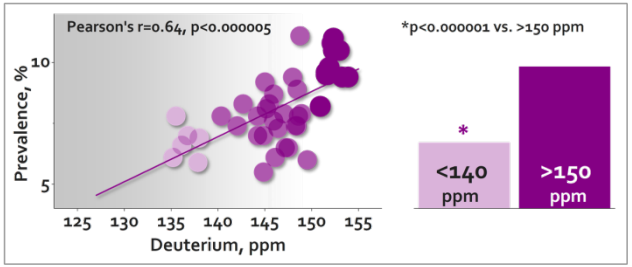
Generally, people who reside at places with deuterium content of water **<140** ppm are healthier compared to those, who live at places with deuterium content of water **>150** ppm.

(see graphs on next slide)

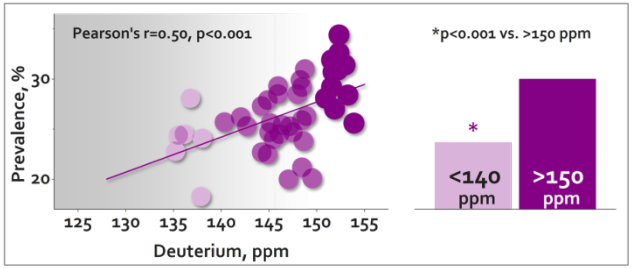
Metabolic disorders

disorder prevalence vs. deuterium content in tap water across U.S.A.

Diabetes, age 18+



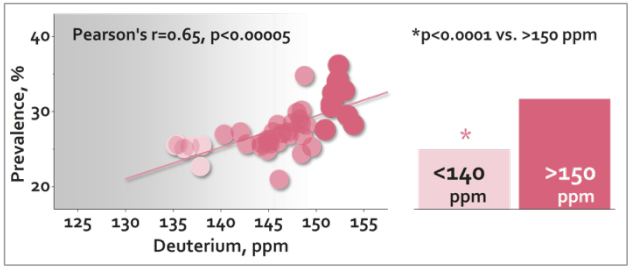
Obesity, age 18+



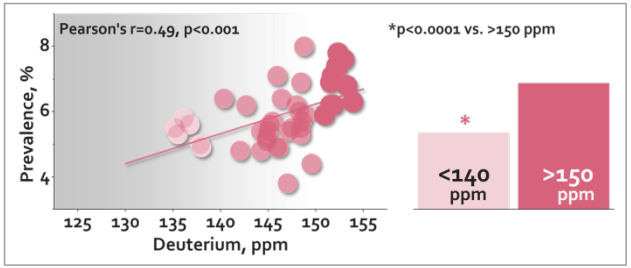
Cardiovascular disorders

disorder prevalence vs. deuterium content in tap water across U.S.A.

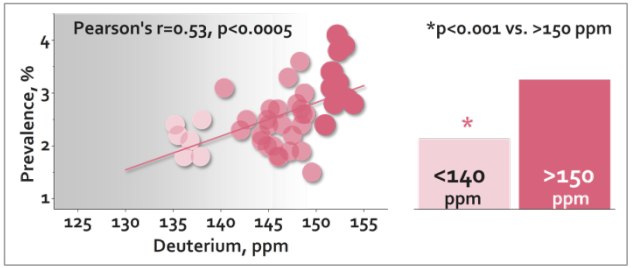
Hypertension, age 18+



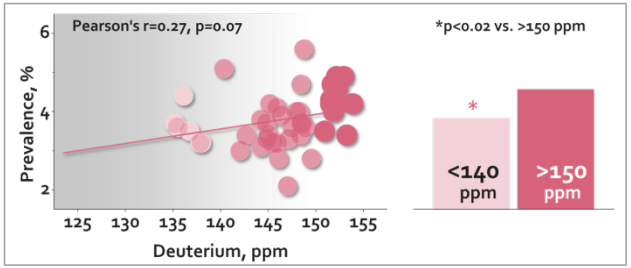
Coronary Heart Disease, age 18+



Stroke, age 18+



Myocardial Infarction, age 18+



Focus on major depression

Major depressive disorder (MDD) is the second leading cause of disability among all diseases on global basis. Lancet 2015, 386(9995):743.

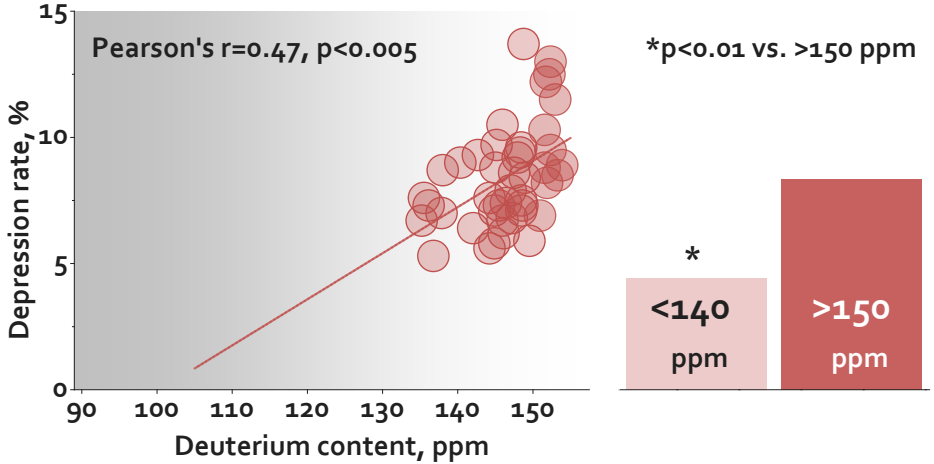
Figure 1 shows that there is a significant correlation between depression prevalence and deuterium content of tap water across continental USA (Pearson's r=0.47, p<0.005). Thus, deuterium content of water increases susceptibility to depression.

By estimation, every 10 ppm of decrease of deuterium content of water leads to decrease in absolute prevalence of depression by 1.8%.

It suggests that:

- ✓ HOD is a depressogenic molecule; and
- ✓ a decrease in HOD intake with water may represent a special nutritional need for subjects suffering from major depression.

Figure 1. Prevalence of depression *vs.* deuterium content of tap water across continental USA



Strekalova et al, Behavioural Brain Res 2015, 277: 237-244.

HOD is depressogenic: experimental evidence

Experiment: Mice receiving either 140 or 91 ppm waters were exposed to 10-days chronic stress and tested on depressive symptoms.

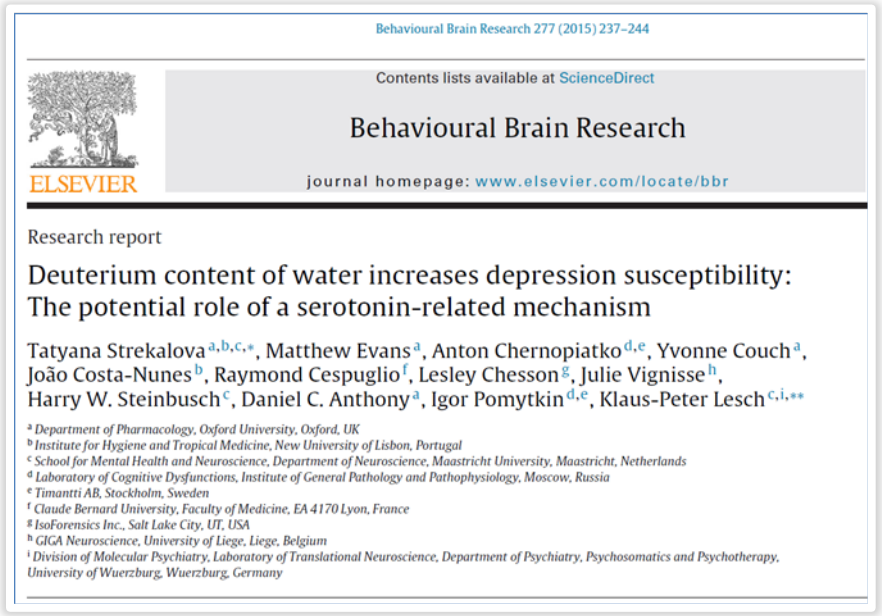
Major findings:

37% and 80% of mice become depressive in 91 ppm and 140 ppm group, respectively, (relative risk 0.46, p=0.014).

Compared to 140 ppm group, mice from 91 ppm group had:

- significantly less depressive symptoms
- significantly higher hippocampal neurogenesis
- significantly less duration of REM sleep
- significantly less (~10-fold) expression of serotonin reuptake transporter (SERT)

Conclusion: in full agreement with above human data, deuterium content of water increases depression susceptibility, i.e. HOD is the depressogenic molecule.



Behavioural Brain Research 277 (2015) 237–244

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Deuterium content of water increases depression susceptibility: The potential role of a serotonin-related mechanism

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Unpublished results

No	Study	Comment
1	Effect of two-week's intake of low deuterium waters (91, 119, 128, and 140 ppm) vs. control water (~150 ppm) or imipramine on depressive-like behavior in 3-month-old male C57Bl/6N mice.	Dose-dependence study
2	Effects of two-week's intake of low deuterium water (91 ppm) vs. control water (140 ppm) on depressive-like behavior in 18-month-old C57Bl6J mice.	Model of elderly depression
3	Effects of two-week's intake low deuterium water (91 ppm) vs. control water (140 ppm) on (i) total expression of genes (Illumina) and (ii) expression of TLR4, TLR2, SERT, COX1, PER2, GSK3 beta, IL1b, TNFa, and NOX2 genes (RT-PCR) in prefrontal cortex and hippocampus of 3-month-old male C57Bl6J mice.	Mechanistic study
4	Effects of two-week's intake of low deuterium water (91 ppm) vs. control water (140 ppm) or citalopram on depressive-like behavior in 3-month-old SERT+/- mice.	Model of antidepressant-resistant depression

EU & US regulations for dietary management of a disease

EU regulation: "Dietary food for special medical purposes" is a food for particular nutritional uses specially processed or formulated and intended for the dietary management of patients and to be used under medical supervision. Commission Directive 1999/21/EC (Article 1 (2b)).

US regulation: "Medical food" is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)).

Key idea:

To develop a food for dietary management of major depressive disorder, which food would retain total adequate intake of water by patients suffering from depression, while reduce daily intake of depressogenic HOD.

Deuterium depleted water as Medical Food for depression: market and competitors

No competition: Psychotherapy, electroconvulsive therapy, antidepressant medication, or other depression treatments cannot replace HOD depleted water in reducing intake of depressogenic HOD during daily water intake. Therefore, there is no competition between HOD depleted water and other technologies for the treatment of depression.

New market: Because of no competition with current depression treatments, HOD depleted water would not take a share of existing market, while would create an additional market of the treatment of depression.

Potential market size: Maximum market size for HOD depleted water would be reached when every patient suffering from depression, during periods of depression, totally replaces daily adequate intake of plain water by the HOD depleted water.

Deuterium depleted water as the product: It is proposed to use water having HOD content from D/H 89 to 120 ppm, conventionally mineralized, for dietary management of depression in amounts of 2-3 liters per day per person suffering from depression.

Cost-effective range: A large scale production of HOD depleted water having HOD content within the range of D/H 89-120 ppm (Antarctic-like water) is cost-effective.

Food regulation: Water having HOD content from D/H 89 to 120 ppm is within natural range of HOD concentrations (D/H 85-175 ppm). Therefore, there is no regulatory requirements to the product besides those established by food regulations.

Patent position

Patent No	Title		Status	Priority date
RU 2482706	Medical food for the dietary management of depression and methods thereof		Granted	2011-12-05
	WO2013085431		Publication	2011-12-05
	EP2787842		Withdrawn	2011-12-05
	CA2858192		Pending	2011-12-05
	AU2012348397		Granted/withdrawn	2011-12-05
	CN103987281	CN 103987281 B	Granted	2011-12-05
	JP2015500832	JP 6134330 B2	Granted	2011-12-05
	KR20140103289	KR 101669741 B1	Granted	2011-12-05
	US20130142883	US 9,220,727 B2	Granted	2011-12-05
RU 2481009	Food for the dietary management of depression/anxiety		Granted	2011-12-05